Cont

19. (New) The compound of claim 17 wherein the critical region is the G3:U70 base pair.

In the Drawing

The applicant acknowledges the Notice of Patent Drawing Objection and will submit new drawings to the U.S. Patent and Trademark Office draftsman when the present application is allowed.

**REMARKS**

The present application is directed to a method for inhibiting RNA function by blocking the minor groove. Sequence information and computer modelling or x-ray crystallography is used to identify the minor groove of the RNA molecule to be inhibited, and a compound is designed that will bind to the nucleotides exposed on the surface of the minor groove. The presence of the compound within the minor groove impairs or prevents replication or other functions essential to the survival of the RNA molecule.

The applicant has amended Claim 11 to to correct a typographical error. Claim 12 was amended to add viral RNA to the group of RNAs claimed. Support for the amendment to Claim 12 can be found on page 6, lines 1 to 7 and in Example 5 starting on page 41 of the specification. New claims 14 to 19 are directed

to inhibition of the $tRNA^{Ala}$ molecule by blocking a critical site in the minor groove such as the G3:U70 base pair as specifically described in the application. Support for these new claims can be found on page 17, lines 10 to 25 and elsewhere throughout the specification, including the Examples.

The Examiner rejected claims 1, 3-5, 7, 8, 11, and 12 under 35 U.S.C. §103 as being obvious on the basis that one could determine the three dimensional structure as taught by Badger et al., *J. Mol. Biol.* 207:163-174 (1980); determine the critical nucleotide sequence in the targeted ribonucleic acid as taught by Endo et al., *J. Biol. Chem.* 265:2216-2222 (1990), Shi et al., *Biochem.* 29:3621 (1990), and Dreher and Hall, *J. Mol. Biol.* 201:41-55 (1988); and synthesize a compound that would bind specifically to the critical site in view of the teachings of Park et al., *Biochem.* 28:2740-2746 (1989), who teach that bound tRNA synthetase protects certain cites in the three dimensional structure of tRNA. The Examiner explained that, although none of the cited publications teach the binding of a compound to the "minor groove" of an RNA molecule, they show or teach the importance of the location of the targeted sequence. Applicant respectfully traverses the Examiner's rejection under 35 U.S.C. §103.

Badger et al. disclose three-dimensional x-ray structures of drug-resistant mutants of human rhinovirus 14, including the antiviral drug-binding "WIN pocket", and compare these structures to those predicted by calculations. Endo et al. teach the interaction of the cytotoxic mold protein alpha-sarcin with a specific site on eukaryotic 28 S rRNA that activates ribosomes. Shi et al. teach that mutations in the G3-U70 base pair in the amino acid acceptor stem of a tRNA molecule affect the efficiency of aminoacylation *in vitro*. Dreher and Hall disclose the inhibitory effects of mutations in the pseudoknot, and the bases of arms B, C and D of the tRNA-like structure of Brome mosaic virus RNA on tyrosylation and adenylation *in vitro*. Park et al. teach that a single G-U base pair substitution in the acceptor helix of a tRNA molecule of *E. coli* affects both the binding rate and the catalytic rate of alanyl-tRNA synthetase, thereby inhibiting aminoacylation.

Applicant agrees with the Examiner that none of the cited publications teach the binding of a compound to a critical site **within the minor groove** of an RNA molecule for inhibition of RNA replication and function as taught in the present application. Furthermore, there is nothing in any of the cited publications that would suggest or imply RNA inhibition by blocking the minor groove with a bound compound. The courts have clearly stated

that "obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching, suggestion or incentive supporting the combination." *In re Geiger*, 2 U.S.P.Q. 2d 1276, 1278 (Fed.Cir. 1987). The applicant respectfully submits that, because none of the references teach, suggest, imply or provide incentive for the binding of a compound within the minor groove, the claimed method of inhibiting RNA cannot be obvious under 35 U.S.C. §103.

The Examiner rejected the specification and claims 1-13 under 35 U.S.C. §112, first paragraph, on the basis that the specification does not provide an enabling disclosure and does not present the best mode for carrying out the invention. The applicant respectfully traverses the Examiner's rejection and submits that the specification enables identification of a critical region within the minor groove of an RNA molecule and the design of a compound that binds to the critical region to inactive the molecule.

In the enclosed Declaration of Paul R. Schimmel Under 37 C.F.R. §1.132, Dr. Schimmel explains recent experiments conducted in his laboratory at the Massachusetts Institute of Technology that were used to identify previously unknown critical sites within the minor groove of an RNA molecule using deoxy and O-methyl substitutions in accordance with the claimed method. The

use of substitutions for determining a critical site is described on page 9, lines 5 to 31 of the specification of the present application. Dr. Schimmel explains that one skilled in the art would be able to conduct similar experiments to identify other critical sites within the minor groove of RNA molecules.

The applicant respectfully submits that the specification clearly enables inhibition of an RNA molecule such as, for example, the $tRNA^{Ala}$ molecule by blocking a critical site such as, for example, the G3:U70 base pair within the acceptor stem of the $tRNA^{Ala}$ molecule. Identification of the G3:U70 base pair as a critical site and its location within the minor groove of the tRNA molecule is described on page 17, lines 10-25 of the specification and in Example 3 starting on page 31 of the specification.

The applicant respectfully submits that, upon identifying the critical site, one could design compounds, such as a mutant or inactive alanine-tRNA synthetase, or a portion thereof, that would bind to the G3:U70 base pair in accordance with methods known to those skilled in the art to effectively block the binding of active alanine-tRNA synthetase within the minor groove, thus inhibiting aminoacylation and mRNA transcription.

With regard to the Examiner's statement that the best mode for a method of designing compounds for inhibiting RNA is not described in the specification, the applicant respectfully submits that a preferred method for designing compounds specifically targeting RNA sequences is set forth on page 5, lines 6 to 9 in the Summary of the Invention.

The best mode requirement of 35 U.S.C. §112 was included in the patent statutes to "restrain inventors from applying for patents while at the same time concealing from the public preferred embodiments of their inventions which they have in fact conceived." *In re Gay* 135 U.S.P.Q. 311, 314-315 (CCPA 1962). The Court of Appeals for the Federal Circuit set forth the following analysis for determining whether an applicant satisfied the best mode requirement: 1) did the inventor, at the time the application was filed, know of a mode of practicing the claimed invention that he considered to be better than any other? 2) if yes, then has the inventor "concealed" his preferred mode from the "public"? *Chemcast Corp. v. Arco Industries Corp.* 16 U.S.P.Q.2d 1033, 1036 (Fed. Cir. 1990). A negative response to the first question is acceptable as stated by the court in *Randomex Inc. v. Scopus Corp.* 7 U.S.P.Q.2d 1050, 1054 (Fed. Cir. 1988) who held that an applicant does not have to point out which embodiment is the best mode.

The applicant respectfully submits that he has not attempted to conceal a preferred method, but, in contrast, has attempted to provide the public with a sufficient number of alternative embodiments to enable the identification of a suitable target RNA sequence, of interest to one reading the application, and the design of a compound that would bind to that sequence. The Examples set forth in the present application describe the identification of several specific target sequences, describe computer modelling systems that can be used to design compounds for inhibition of those and other sequences, describe methods for the synthesis of such compounds, and describe methods for delivery of inhibitory compounds to the targeted RNA molecule.

Applicant respectfully submits that he should not be penalized for providing the public with these alternative embodiments.

The Examiner rejected claims 1-10 under 35 U.S.C. §112, second paragraph, on the basis that the function of the bound compound is not clear in view of the Park et al. publication. The Examiner suggests that Park et al. teach that substrate binding does not necessarily cause RNA inhibition. Applicant cannot find a statement or figure within the Park et al. paper making this conclusion. In the abstract of the Park et al. publication, the authors state that, at physiological conditions,

high concentration of the mutant A3-U70 tRNA molecule does not inhibit aminoacylation of a **wild-type** alanine tRNA. Park et al. conclude that substitution of $G^3$ by $A^3$ in the mutant causes a decrease in the affinity of alanyl-tRNA synthetase for the tRNA molecule binding site (an increase in Km). The applicant respectfully submits that this observation confirms that the blockage of a binding site, such as the minor groove, by a compound selected in accordance with the claimed method, would most likely prevent the binding of an enzyme necessary for RNA function.

In view of the foregoing remarks, allowance of pending claims 1, and 3-19 is respectfully requested.

Respectfully submitted,

Jamie L. Greene
Reg. No. 32,467

Dated: July 28, 1992

KILPATRICK & CODY
Suite 2800
1100 Peachtree Street
Atlanta, GA 30309-4530
404/815-6608